Full Text PA-96-053

GENDER IN THE PATHOGENESIS OF AUTOIMMUNITY: MECHANISMS

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National Institute of Allergy and Infectious Diseases
National Institute of Neurological Disorders and Stroke
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National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Dental Research
Office of Research on Women's Health

PURPOSE

The National Institute of Allergy and Infectious Diseases gives special consideration for funding to scientifically meritorious applications in response to Program Announcements. Program Announcements identify areas of ongoing research emphasis for the NIAID.

The National Institute of Allergy and Infectious Diseases (NIAID),
National Institute of Neurological Disorders and Stroke (NINDS),
National Institute of Diabetes, Digestive and Kidney Diseases
(NIDDK), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Dental Research (NIDR), and the Office of Research on Women's Health (ORWH) invite applications for basic studies that will increase knowledge of the mechanisms by which gender influences the development of autoimmune disease and the regulation of the immune response in individuals with these diseases. Although it is clear that autoimmune diseases disproportionately affect women, the reasons for this are not clear. Research into the basic mechanisms by which sex hormones or non-hormonal gender differences affect the immune

response and protect from or contribute to a break in self tolerance should allow for the development of improved therapeutic and preventive strategies for autoimmune disease.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This Program Announcement (PA), Mechanism of Gender's Effect in Pathogenesis of Autoimmunity, is related to the priority area of diabetes and chronic disabling diseases. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0 or Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-0325 (telephone 202-512-1800).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators. Foreign institutions are not eligible for the First Independent Research Support and Transition (FIRST) award.

MECHANISM OF SUPPORT

Traditional research project grant (R01), FIRST (R29), and small research grants (R03) may be submitted in response to this announcement. The total project period for an application submitted in response to this PA may not exceed five years; a foreign application may not request more than three years of support.

NIAID uses R03 grants to support small highly innovative or pilot projects. Applicants for R03 grants may request up to $50,000 annual direct costs for a period not to exceed three years. Funds and time requested should be appropriate for the research proposed. Applicants for R03 grants must follow the special application guidelines available from the program staff listed under INQUIRIES.

NINDS and NIAMS do not utilize the R03 mechanism.

RESEARCH OBJECTIVES

Background

Autoimmune diseases, which disproportionately affect women, are a significant source of morbidity, often severe, in the population, costing billions of dollars annually in health care expenses and lost productivity. Systemic lupus erythematosus (SLE) affects women seven to nine times more frequently than men; Sj"gren's syndrome is found nine times as frequently in women; multiple sclerosis is twice as common in women; rheumatoid arthritis is three to four times as common; and autoimmune thyroid disease, including both thyroiditis and Grave's disease, is six to ten times as common in women as men. Many of these diseases increase in frequency after puberty, suggesting a role for sex hormones in their pathogenesis. However, autoimmune disease is also more common in prepubertal females than prepubertal males. Furthermore, pregnancy may exacerbate the course of some autoimmune diseases, while it ameliorates the course of other autoimmune diseases. Thus, factors other than sex hormones may be important in modulating the immune response in these diseases. Both human and animal studies suggest that the genetic background plays a significant role in the development of autoimmune disease. For example, although estrogens have been shown to accelerate the development of autoimmune disease in certain inherited animal models of SLE, and testosterone has been shown to inhibit the onset of disease in these same models, other models of SLE show minimal effects of sex hormones, suggesting an interaction of genetic and hormonal influences on the immune response. Additionally, data in both humans with multiple sclerosis and an animal model of this disease suggest differences in the response of males and females in the development of tolerance after feeding of oral antigens, implying that the efficacy of immunotherapies may be in part gender associated.

A recent NIH-sponsored meeting on GENDER AND AUTOIMMUNITY reviewed the state of current knowledge concerning the reasons women disproportionally are afflicted by autoimmune diseases and identified several areas in which further research is needed. The role of sex hormones in modulating the normal and autoreactive immune response is not clear and more information is needed at the molecular and cellular level. Non-hormonal influences of gender, including imprinting, genetic, and environmental factors may also be important, but are not clearly defined. The breakdown of tolerance to self is a key component of autoimmune diseases, yet the mechanisms by which gender affects the development, maintenance, or loss of tolerance are unknown.

Objectives and Scope

This PA will support basic research on the role of gender in the pathogenesis of autoimmunity and autoimmune diseases. Relevant topics include, but are not limited to:

o the role of non-hormonal intrinsic aspects of gender, including X-chromosome inactivation and other genetic/chromosomal factors in regulating the immune response;

o neuroimmunological and neuroendocrine influences on the development of an autoreactive response;

o genetic influences on the immune response of males versus females;

o examination of the effects of sex hormones on the immune response at the molecular and cellular level. Examples include: sex hormone effects on T cell subset differentiation, i.e., Th1 versus Th2; cytokine networks; thymic selection; B cell repertoire development and activation; antigen presenting cell function and cellular trafficking;

o mechanism(s) by which the autoreactive immune response is altered during pregnancy and in the post partum period;

o the role of imprinting in the development of autoimmune disease; and

o mechanism(s) by which gender regulates the response to therapies for autoimmune disease.

The above examples of research topics and approaches are not meant to be all inclusive or restrictive. Investigators are encouraged to develop their own innovative hypothesis-driven approaches to achieve the goals of this PA.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This new policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43) and supersedes and strengthens the previous policies (Concerning the Inclusion of Women in Study Populations, and Concerning the Inclusion of Minorities in Study Populations), which have

been in effect since 1990. The new policy contains some provisions that are substantially different from the 1990 policies.

All investigators proposing research involving human subjects should read the "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research," which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and printed in the NIH Guide for Grants and Contracts, Volume 23, Number 11, March 18, 1994.

Investigators also may obtain copies of the policy from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

APPLICATION PROCEDURES

Applicants are strongly encouraged to call program staff early in project development with any questions regarding the responsiveness of their proposed project to the goals of this PA. Applications are to be submitted on the grant application form PHS 398 (rev. 5/95) and will be accepted on the standard application deadlines as indicated in the application kit. Application kits are available at most institutional offices of sponsored research and may be obtained from the Grants Information Office, Office of Extramural Outreach and Information, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone (301) 435-714, email: asknih@odrockm1.od.nih.gov.

Each application must be identified by checking "YES" on line 2 of the PHS face page, and the number and title of this program announcement must be typed in section 2.

The completed original and five legible, single-sided copies of the application must be sent or delivered to:

DIVISION OF RESEARCH GRANTS
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040, MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817-7710 (for express/courier service)

R03 APPLICANTS ONLY: Direct inquiries regarding review issues and special instructions for application preparation and mail two copies of the R03 application and all five sets of any appendices to:

Stanley Oakes, Ph.D.
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases
Solar Building, Room 4C06
6003 Executive Boulevard
Bethesda, MD 20892-7610
Telephone: (301) 496-7042
FAX: (301) 402-2638
Email: stanley_oaks@nih.gov

FIRST (R29) applications must include at least three sealed letters of reference attached to the face page of the original application. FIRST applications submitted without the required number of reference letters will be considered incomplete and will be returned without review.

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the Center as a resource for conducting the proposed research. If so, a letter of agreement from the GCRC Program Director must be included in the application material.

REVIEW CONSIDERATIONS

Applicants for all Small Research (R03) grants must see the REVIEW CONSIDERATIONS section of the notice "SMALL RESEARCH GRANTS - NIAID," which appeared in the NIH Guide for Grants and Contracts, Vol. 22, No. 9, March 22, 1996, and are available from the NIAID program staff listed under INQUIRIES.

Applications will be assigned on the basis of established PHS referral guidelines. Applications will be reviewed for scientific and technical merit in accordance with the standard NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally about 50 percent of applications under review, will be discussed, assigned a priority score, and receive a second level review by the appropriate national advisory council.

Review Criteria

o scientific, technical, or medical significance and originality of proposed research;

o appropriateness and adequacy of the experimental approach and methodology proposed to carry out the research;

o qualifications and research experience of the Principal Investigator and staff, particularly, but not exclusively, in the area of the proposed research;

o availability of the resources necessary to perform the research;

o appropriateness of the proposed budget and duration in relation to the proposed research;

o adequacy of plans to include both genders and minorities and their subgroups as appropriate for the scientific goals of the research.

The initial review group will also examine the provisions for the protection of human and animal subjects and the safety of the research environment. Concerns expressed by the initial review group about any of these factors may influence the recommendation of the National Advisory Allergy and Infectious Diseases Council concerning funding of that application.

AWARD CRITERIA

The following will be considered when making funding decisions: quality of the proposed project as determined by peer review, program balance among research areas of the program announcement, and availability of funds.

INQUIRIES

Written and telephone inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

Elaine Collier, M.D.
Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases
Solar Building, Room 4A20
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Bethesda, MD 20892-7640
Telephone: (301) 496-7104
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A. P. Kerza-Kwiatecki, Ph. D.
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FAX: (301) 402-2060
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Ronald Margolis, Ph.D.
Division of Diabetes, Endocrinology and Metabolic Diseases
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Susana Serrate-Sztein, M.D.
Arthritis Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
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Eleni Kousvelari, D.D.S., D.Sc.
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Direct inquiries regarding fiscal matters to:

Mrs. Pamela Fleming
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National Institute of Allergy and Infectious Diseases
Solar Building, Room 4B30
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Ms. Carol Fitzpatrick

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AUTHORITY AND REGULATIONS

This program is supported under authorization of the Public Health Service Act, Sec. 301 (c), Public Law 78-410, as amended. The Catalogue of Federal Domestic Assistance Citation is No. 93.855 - Immunology, Allergy, and Transplantation Research, No. 93.853 - Clinical Research of Neurological Disorders and Stroke, No. 93.847 - Diabetes, Endocrinology, and Metabolic Diseases, No. 93.121 – Oral Diseases and Disorders Research, and No. 93.846 - Arthritis, Musculoskeletal and Skin Diseases Research. Awards will be administered under PHS grants policies and Federal Regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Return to PA Index
Return to NIH Guide Main Index